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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,678	11/28/2000	Kan-Hung Lee	TAI-3L6	7845

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,678	LEE ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *6-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1-26 are pending in the instant application. Claims 6-20 have been withdrawn from consideration as being drawn to a non elected invention. Claims 1-5 and 21-26 are currently under consideration. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112

3. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is indefinite as it is unclear how the kit further comprises at least one synthetic nucleotide sequence according to claim 5, however, the limitations of claim 23 are such that specific combinations of primers according to claim 1, ie: SEQ ID NO 1 and SEQ ID NO 6, would result in no synthetic nucleotide sequences according to claim 5 present in the kit. It is further noted that in such case, claim 23 does not further limit claim 22.

Response to Arguments

The response traverses the rejection. The response asserts that the additional feature i.e. "at least one synthetic nucleotide sequence according to claim 5" over the features reflected in claims 22 and 21 are present in claim 23. The response then states "Because of the dependence of claim 23 on claim 22, the features claimed in claims 23 including: 'more than one pair of oligonucleotide primers according to claim 1, and at least one synthetic nucleotide sequence according to claim 5, where the pairs of oligonucleotide primers are limited as defined in claim 21." The response further recites "no limitations or restrictions in claims 1, 5, 21, or 22 preclude any of the synthetic nucleotide sequences in claim 5 being present in the kit claimed in claim 23". These arguments have been thoroughly reviewed but were found unpersuasive. Firstly, the sentence "Because of the dependence..." is unclear and it appears that the sentence is unfinished. Secondly, keeping in mind that the limitations from claims 1, 5, 21, and 22 are in claim 23 due to the chain of dependency, it is not these limitations that cause the problem with claim 23, but the recitation within claim 23 itself. Claim 23 is confusing as it contains two recitations with double negatives. If one were to following the directions from claim 23, it appears that if any primer pairs from claim 1 (ie primer pairs SEQ ID NO 1 and SEQ ID NO 6, and SEQ ID NO 2 and SEQ ID NO 6, for example) are present that are not SEQ ID NO 5 and SEQ ID NO 8, then none of the synthetic nucleotides from claim 5 are present in the kit. There are no directions in any of the previous claims from which claim 23 depends, that stipulate the presence of SEQ ID NO 5 and SEQ ID NO 8. The only stipulation in claims 1 and 21 are that if SEQ ID NO 5 is present, then SEQ ID NO 8 is paired with it, however, SEQ ID NO 5 need not be present in any of the claims as the claims recite the primers of the pairs in the alternative. Since claim 23 stipulates that at

least one synthetic nucleotide sequence from claim 5 be present in the kit, claim 23 is indefinite as it appears that there are situations where no synthetic nucleotide sequences would be present, therefore, in certain situations, the claim cannot meet it's own limitations. In such a case, claim 23 does not further limit claim 22. For these reasons and the reasons made of record above, this rejection is maintained.

Claim Rejections - 35 USC § 103

4. Claims 1-5 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilpatrick (US Patent 6,168,917: 102(e) date July 9, 1999) in view of Accession numbers U22521 (Jan 1997), AF177911 (Sep 1999), AF136379 (Jun 2000), U55870 (May 1996) and Z78129 (Aug 1997) and further in view of Accession number E30248 (from JP 1999346799, published Dec 1999).

Kilpatrick teaches a method that uses specific primer pairs to detect different enterovirus serotypes, including enterovirus 71 and coxsackievirus A16 (see col.2, fig 5, col 11, table 1, and cols 16 and 17). Kilpatrick specifically teaches that there is a need for a detection system that identifies and differentiates most or all enterovirus serotypes and that such would improve the speed and accuracy of processing samples and increase the sensitivity of detecting minority populations of enteroviruses in mixed serotype cultures (col. 6, lines 31-35). Kilpatrick specifically teaches methods of developing suitable primer pairs, including the use of degenerate primer pairs which incorporate mixed base residues or deoxyinosine to increase the speed and sensitivity of detecting non polio enteroviruses (col. 7, lines 40-41, and col 15). Kilpatrick teaches an amino acid alignment of different non polio enteroviruses including enterovirus 71

and coxsackievirus A16 (fig 2a-2d) and further teaches that nucleotide sequences of such were known at the time of the invention (col. 10, lines 16-30). Kilpatrick teaches how to develop specific primer pairs to identify such serotypes in PCR based methods of detection and differentiation (col 11-13) using regions of differing nucleic acid sequence homology among nucleotide capsid sequences (col 12, lines 26-67 and col 10 lines 31-32) of different serotypes. Further, Kilpatrick teaches providing such primer pairs in kit format for use in practicing the method of Kilpatrick (para bridging cols 13 and 14). It is noted that Kilpatrick does not teach primer pairs or kits comprising the claimed primer sequences. However, the sequence of enterovirus 71 and coxsackievirus A16 were known in the art at the time of the invention, and specifically the following Accession numbers were available to the ordinary artisan: U22521 teaches the complete sequence of Enterovirus 71 BrCr, AF177911 teaches the coxsackievirus A16 polyprotein gene (which contains SEQ ID NO 14: positions 1346-1475, and SEQ ID NO 15, positions 1392-1422), AF136379 teaches Enterovirus 71 polyprotein mRNA, U55870 teaches an Enterovirus 5' non translated region sequence which contains SEQ ID NOS 10 and 11 and Z78129 teaches a region of Enterovirus 70 RNA 5' untranslated region (which contains SEQ ID NO 9). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to develop primer pairs and nucleotide sequences to detect Enterovirus 71 and Coxsackievirus A16 and to package such sequences in kit format as Kilpatrick specifically teaches primer pairs that detect specific serotypes including Enterovirus 71 and Coxsackievirus A16 and teaches packaging such in kit format. The ordinary artisan would have been motivated to develop such sequences as Kilpatrick specifically teaches a need for such a system. Although Kilpatrick in view of the recited accession numbers do not teach the

specific primer pair and nucleotide sequences of the claimed invention, armed with the teachings of Kilpatrick, the ordinary artisan would have been able to develop primer pairs and nucleotide sequences that would specifically detect Enterovirus 71 and Coxsackievirus A16 given that the sequences of such serotypes were known in the art at the time of the invention and Kilpatrick specifically teaches how to develop specific primer pairs and nucleotide sequences specific for certain serotypes (it is noted that accession number E30248 teaches the reverse complement of SEQ ID NO 7, which is used to identify serotypes of enterovirus). Such primer pairs and nucleotide sequences would be considered functionally equivalent in a method of detecting Enterovirus 71 and Coxsackievirus A16, absent evidence to the contrary.

Response to Arguments

The response traverses the rejection. The response asserts that the present application relates to conserved portions in the nucleic acids of known pathogenic enteroviruses, which were identified by the present invention for the first time. The response further asserts that since Kilpatrick was not aware of the existence of the conserved portions among the enteroviruses according to the present invention, no evidence indicates that a person skilled in the art could devise the primers of claim 1 based on the conserved portions, much less the kits of claims 21-26. These arguments have been thoroughly reviewed but were found unpersuasive for the following reasons. Firstly, it is noted the sequences of many different enteroviruses, including enterovirus 71 and coxsackievirus A 16, which are enteroviruses used in the presently claimed invention, were known and their sequences (via accession numbers) are disclosed by Kilpatrick (see col. 10, lines 16-30). Further, the previous office action cited additional sequences from the enteroviral genome to illustrate that sequences pertaining to the enteroviral genome were well

known at the time the application was filed. Secondly, the state of the art at the time of the invention was high with regard to detecting conserved and variable genomic regions between different species and strains of microorganisms and using primers to conserved regions to identify common strains of microorganisms, as well as probes to species and strain specific regions to differentiate different species or strains from one another. Kilpatrick illustrates this and teaches a method that targeted a conserved region within the enteroviral genome, primers with degenerate sequences to first detect the enteroviruses, as well as sequence specific probes to differentiate specific species and strains from one another. Although the region targeted by Kilpatrick is not the same as that targeted by the presently claimed primers and probes, Kilpatrick teaches that sequence identities for different enteroviruses are more than 50% over the whole genome, and that within species, the sequence identity is over 75% over the whole genome (col. 2, lines 35-39). Therefore, the ordinary artisan would have had a reasonable expectation of success that other regions in the enteroviral genome existed that were conserved. Given that the sequences of the genome of many enteroviruses were already sequenced and readily available, it would have been well within the skill of the ordinary artisan to align these known sequences and identify conserved and variable regions. The ordinary artisan would have been motivated to construct primers and probes to detect and differentiate between species of enteroviruses, such as enterovirus 71 and coxsackievirus A16 as Kilpatrick teaches a need for efficient and sensitive diagnostic assays for detecting and classifying enteroviruses, including these specific species. It is further noted that the instant claims are broadly drawn to a larger number of different primer pairs or synthetic oligonucleotides than the specific sequences of nucleotides recited in the claims as the claims also recite sequences "comprising" or "comprising

conserved portions" of the recited SEQ ID NOS, as well as degenerate sequences (for primers which target coding regions). Further, a majority of the claimed sequences contain variability in the form of "R", "Y", and "H", (mixed bases) for example, which do not limit the identity of a nucleotide at certain positions to a specific purine or pyrimidine. In the recent court decision *In re Duel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. However, regarding structural and functional homologues, the court stated

> "Normally, a prima facie case of obviousness is based upon structural similarity, ie, an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try and obtain compounds with improved properties."

The claimed oligonucleotide probes and primers represent structural homologues with similar properties to the sequences disclosed by Kilpatrick. The sequences are from conserved portions of the enteroviral genome and are used in methods of detecting and differentiating enteroviruses species from each other. A biochemist of ordinary skill in the art would be motivated to and attempt to obtain alternate compounds with improved properties. Such analysis is considered well within the skill of the ordinary artisan as the nucleic acid sequences of the enteroviral genome, including the sequences targeted by the instantly claimed probes and primers, were sequenced and readily available at the time the invention was made. Further, the teachings of Kilpatrick provide the ordinary artisan with a reasonable expectation of success that structural and functional homologues of the primers and probes developed by Kilpatrick could be made. The claimed primers and probes are therefore prima facie obvious over the cited references in the

absence of secondary considerations. For these reasons and the reasons made of record above, this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

5. Claim 5 is rejected under 35 U.S.C. 102(a) as being anticipated by Accession number AF136379 (June 2000).

Claim 5 has been amended to recite "or a nucleic acid comprising the sense strand". AF136379 teaches a sequence of 7410 nucleic acids which comprises SEQ ID NO 13 (positions 1456-1483) and SEQ ID NO 14 (positions 1392-1421). AF136379 is a sequence that is the complete CDS for enterovirus 71 isolate NCKU9822 polyprotein, and would hybridize specifically to an enterovirus sense strand or a nucleic acid comprising the sense strand. It is further noted that the limitation of "synthetic nucleotide construct" does not carry patentable weight to distinguish the claimed sequences over that of AF136379.

6. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Accession number Z78129 (August 1997).

Claim 5 has been amended to recite "or a nucleic acid comprising the sense strand". Z78129 teaches a sequence of 358 nucleic acids which comprises SEQ ID NO 9 (positions 260-286). Z78129 is a sequence that is part of the 5' untranslated region of Enterovirus 70, strain B2592, and would hybridize specifically to an enterovirus sense strand or a nucleic acid comprising the sense strand. It is further noted that the limitation of "synthetic nucleotide construct" does not carry patentable weight to distinguish the claimed sequences over that of Z78129.

7. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Accession number U55870 (May 1996).

Claim 5 has been amended to recite "or a nucleic acid comprising the sense strand". U55870 teaches a sequence of 83 nucleic acids which comprises SEQ ID NO 10 (positions 15-47) and SEQ ID NO 11 (positions 48-75). U55870 is a sequence that is part of the 5' NTR sequence of an enterovirus species, would hybridize specifically to an enterovirus sense strand or a nucleic acid comprising an enterovirus sense strand. It is further noted that the limitation of "synthetic nucleotide construct" does not carry patentable weight to distinguish the claimed sequences over that of U55870.

Response to Arguments

The response traverses the rejections. The response asserts that even though the genome (or their part) of some enterovirus strains have been sequenced and published, the state of the art at the time this application was filed neither taught nor suggested the conserved portions that were identified in the present application for the first time. The response concludes that therefore, a person skilled in the art would have not way to anticipate the conserved portions, much less the synthetic nucleotide sequences of claim 5, which were first derived from the conserved portions among various enteroviruses according to the present invention. This argument has been thoroughly reviewed but was found unpersuasive because the origin of the sequences of claim 5, that is where they were isolated from, bears no weight over the disclosure of the sequences themselves. Each of the references cited as anticipatory, encompass every feature of the claimed invention. The sequences cited comprise the indicated SEQ ID NOS, and therefore meet the limitation of "a nucleotide *comprising* a conserved portion in the nucleic acids

of enteroviruses" because the recitation of 'comprising' encompasses sequences on either side of the conserved portions. The recitation of "conserved portion" is not sufficient to overcome the teachings of the cited prior art as the claim does not teach where these conserved portions are relative to any sequences and the only structural limitation set forth by the claim is the sequences themselves. Further, as the cited prior art references are all sequences from enteroviruses, all would be able to hybridize to a sense strand of an enterovirus or a sequence comprising the sense strand of an enterovirus.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claims are allowable over the cited prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
5/16/03